UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,226	08/19/2003	Ashley I. Bush	0609.4810002	3164

26111 7590 10/31/2007

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
DUTT, ADITI	
ART UNIT	**PAPER NUMBER**
1649	

MAIL DATE	DELIVERY MODE
10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/643,226	BUSH ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,37 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,37 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 August 2007 has been entered.

Status of Claims

2. The amendment filed on 31 August 2007 has been entered into the record and have been fully considered.

3. Claim 36 is amended. New claims 39-42 are added.

4. Claims 36-37, 39-42, drawn to a method of identification of an agent that inhibits the redox reactive metal-mediating cross-linking of Aβ (amyloid beta peptide), are being considered in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

5. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (31 August 2007).

6. Rejection of claims 36-37, under 35 U.S.C. 112, first paragraph, lack of enablement is withdrawn, because of amendment of the claims, and Applicant's arguments that were found to be persuasive.

Claim rejections maintained/new grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 36-37, 39-42, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 36 and 42 recite the limitation "candidate agent" in steps (d) and (g) of the claims, whereas the preamble reads "an agent". There is insufficient antecedent basis for this limitation in the claim.

9. Claims 37, 39-41 are indefinite as they depend from the rejected indefinite claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 36, 39, 40 and 41, are rejected under 35 U.S.C. 103(a) as being unpatentable over Dyrks et al. (Journal of Biological Chemistry 267, page 18210-18217, 1992), in view of Bush et al. (Science 265: 1464-1467, 1994), and Mantyh et al. (J Neurochem 61: 1171-1174, 1993).

13. The claims are drawn to a method of identification of an agent that inhibits the redox-reactive metal mediated cross-linking of Aβ, by incubating the Aβ samples and the redox reactive metal, in the presence or absence of the agent, (claim 36), wherein the samples are a biological fluid like the cerebrospinal fluid (CSF) (claims 39-40), and the redox-reactive metal is Cu(II) or Fe(III) (claim 41).

14. Dyrks et al teach the aggregation of amyloid beta peptide – Aβ (referred to as βA4 in the reference), and its precursor A4CT (COOH terminal amyloid precursor protein fragment comprising the complete sequence of βA4 peptide at the N-terminal position) (abstract). Dyrks et al further teach the incubation of a (first) sample of A4CT or βA4 with a redox-reactive metal ferrous chloride ($FeCl_2$) for 1 hour at 37°C (figures 3 and 7). Still further, the reference teaches the incubation of A4CT with hemoglobin or FeCl2 (comprising a second sample), in the presence or absence of radical scavengers like ascorbic acid or a vitamin E derivative, which result in the inhibition of protein cross-linking (page18213, figure 4 and page 18214, para 1). It is well-known that iron in the form of Fe(II) or Fe(III), is a major component of hemoglobin.

15. Dyrks et al. do not teach the inhibition of the aggregation of βA4 or Aβ peptide.

16. Bush et al. teach the incubation of human Aβ1-40 peptide in the presence or absence of Zn^{2+} ions or the chelating agent EDTA, for 30 minutes at 37'C, thereafter filtering the solutions through 0.2 μm filters. The reference further demonstrates that Zn causes an aggregation of about 80% of the peptide, which is detected at a concentration of as low as 0.8 μM (Figure 1, page 1465; column 1, para 4). Bush et al. also teach that in the presence of EDTA, human Aβ1-40 did not elicit any distinguishable aggregation (page 1465, Figure 2A).

17. Bush et al. do not teach the incubation of the second Aβ sample with a metal, and an agent that inhibits the metal induced aggregation of Aβ peptide.

18. Mantyh et al. teach the increased aggregation of human βA41-40 by incubating with metal ions such as Fe^{3+}. The addition of excess EDTA to the metal ion containing solution, prevented the ion-induced aggregation of βA4 peptide (Materials and Methods; Figure 1). The reference further demonstrates that iron induced aggregation of βA4(1-40) at a concentration of 10^{-10} M in the CSF, is significantly higher than the control values in the absence of metal ions (Figure 3).

19. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of inhibiting the FeCl2 induced A4CT cross-linking with agents like ascorbic

acid or vitamin E, as taught by Dyrks et al., for the identification of an agent that inhibits the metal induced aggregation of Aβ peptide as taught by Bush et al. or Mantyh et al. The person of ordinary skill in the art would have been motivated to use the method for the inhibition of Aβ aggregation, because it is well established that the Aβ isoforms (such as Aβ1-40), produced by the cleavage of the amyloid precursor protein, are implicated in the plaque formation in disease states. Secondly, the initial aggregation of βA4 by metal ions would contribute to an early step in amyloidogenesis, and several amino acid residues in βA4 are capable of interaction with the metal ions (Mantyh et al, page 1173, last para). Furthermore, as Mantyh et al demonstrate, that the metal induced aggregation of Aβ peptide, is very relevant in vivo, such as in the CSF, which contains a concentration of ~6 X 10^{-10} M of the peptide (similar to that exemplified in Figure 3 (page 1173). Finally, in the concluding paragraph, Dyrks et al (page 18216) suggest that metal mediated reactions lead to insoluble amyloid protein aggregates involved in the pathology leading to Alzheimer's disease. The person of ordinary skill in the art would have expected success because the method of inhibiting the formation of metal induced aggregates by agents such as antioxidants or chelators, was well known in the art at the time the invention was made.

20. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

21. Claims 36, 37, 39-42, are rejected under 35 U.S.C. 103(a) as being unpatentable over Dyrks et al. (Journal of Biological Chemistry 267, page 18210-18217, 1992), in view of Bush et al. (Science 265: 1464-1467, 1994), and Mantyh et al. (J Neurochem 61: 1171-1174, 1993).

22. The claims are drawn to a method of identification of an agent that inhibits the redox-reactive metal mediated cross-linking of Aβ, by incubating the Aβ samples with a redox-reactive metal, in the presence or absence of the agent, followed by the determination of Aβ cross-linking by Western blot (claims 36 and 37), wherein the samples are a biological fluid like the cerebrospinal fluid (CSF) (claims 39-40), and the redox-reactive metal is Cu(II) or Fe(III) (claim 41, 42).

23. The teachings of Dyrks et al., Bush et al., and Mantyh et al. are set forth above.

24. Dyrks et al. further teach, that the insoluble aggregates of βA4 peptide are generated by a metal-catalyzed cross-linking (page 18214, figure 7). Dyrks et al also teach that the βA4 bearing amyloid precursor fragment (A4CT) aggregates, generated by metal catalyzed cross-linking

are causes for amyloid plaques in AD (page 18216, last para), and that such aggregates can be analyzed by Western blot (page 18214, figure 5).

25. Dyrks et al, Bush et al. or Mantyh et al. do not teach the active step comprising the analysis of βA4 protein cross-linking by Western blot.

26. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to look for the presence or absence of βA4 cross-linking as disclosed by Dyrks et al, Bush et al., or Mantyh et al., for the purpose of identifying an agent that inhibits metal-mediated crosslinking of βA4 peptides, using Western blot assay with a reasonable expectation of success. One would be motivated to look for βA4 protein (Aβ) cross-linking, because Dyrks et al teach that the metal induced A4CT aggregates can be analyzed by Western blot, and further disclose that A4CT is an amyloid precursor peptide fragment comprising the complete sequence of βA4 protein at the N-terminal position (abstract-page 18210; results-page18212). The person of ordinary skill in the art would have expected success because the Western blot analysis was a fairly established technique at the time the invention was made.

27. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

28. No claims are allowed.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
27 September 2007

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600